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Clinical characteristics of leg restlessness in Parkinson's disease compared with idiopathic Restless Legs Syndrome

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ABSTRACT

Objective: There is limited data on motor restlessness in Parkinson's disease (PD). Here we evaluate for clinical differences between cohorts of idiopathic Restless Legs Syndrome (iRLS), PD patients with leg restlessness, and PD with RLS.
Methods: We examined 276 consecutive PD patients for leg restlessness symptoms, we compared clinical features of PD patients with RLS, PD patients with leg restlessness but not meeting RLS criteria, PD patient without RLS and iRLS.
Results: A total of 262 PD patients who satisfied the inclusion criteria were analyzed. After excluding 23 possible secondary RLS or mimics, 28 were diagnosed with RLS and 18 with leg motor restlessness (LMR). Compared with iRLS patients, PD patients with RLS or LMR had older age of RLS/LMR onset, shorter duration of leg restlessness, less positive family history, different seasonal trends and more unilaterality of leg restlessness symptom ($P < 0.01$) which were often in accordance with dominant Parkinsonism side and related with Parkinsonism severity. PD patients with RLS/LMR had lower daily dosage ($P < 0.01$) and shorter duration ($P < 0.05$) of dopaminergic medication when RLS/LMR symptom onset than PD without leg restlessness. PD with LMR had less severe Parkinsonism ($P < 0.05$) and leg restlessness ($P < 0.01$) symptoms than PD with RLS.
Conclusion: Clinical characteristics of PD patients with RLS and LMR were different from iRLS, differentiating these various subtypes can facilitate optimal treatment.

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1. Introduction

Restless Legs Syndrome (RLS) and Parkinson's disease (PD) are common neurological disorders that both respond to dopaminergic therapy. Previous prevalence studies showed an association of the two conditions with various reported incidence that varied from 0% to 50% often considered as due to ethnic differences [1–18]. However, most of the previous studied didn't exclude secondary RLS [3,5–14,16–18]. Leg motor restlessness (LMR), which is recently regarded as a kind of "focal akathisia" [19], was described in 2011 as a desire to move the limbs usually associated with paresthesias/dysesthesias but not fulfilling the full RLS criteria [2]. LMR can be a kind of RLS mimic since lower limb restlessness and/or sensory symptoms are frequent manifestations during off periods in PD and are part of the spectrum of levodopa-related fluctuations [20]. Dopaminergics can also affect RLS presentation with controversial effects of either masking or augmenting possible coexisting RLS symptoms. Current literature on the clinical profile of "genuine" leg restlessness in PD and possible overlap confounders is limited, while to discriminate these different conditions is of great importance due to different subsequent therapeutic options. With this background, we studied the clinical spectrum of leg restlessness including RLS and LMR in PD patients and further compared with idiopathic RLS (iRLS) patients to explore the relationship between RLS and PD and to explore if RLS in PD is secondary to Parkinsonism related factors or anti-Parkinsonism medications in a Chinese cohort of patients.

2. Materials and methods

2.1. Subjects

Consecutive outpatients with a diagnosis of PD were recruited from Parkinson's disease and Movement Disorders Clinic in Department of Neurology, Shanghai General Hospital, Shanghai Jiao Tong University

Abbreviations: IRLSRS, International Restless Legs Syndrome rating scale; IRLSSG, International Restless Legs Syndrome Study Group; LED, Levodopa equivalent dosage; LMR, leg motor restlessness; PD, Parkinson's disease; PD/LMR, PD patients with LMR; PD/RLS, PD patients with RLS; RLS, Restless Legs Syndrome; UPDRS III, Unified Parkinson's Disease Rating Scale motor scale.

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School of Medicine between Sep 2012 and Sep 2014. We also collected iRLS patients between Nov 2013 and Sep 2014. PD was diagnosed according to the United Kingdom PD Society Brain Bank clinical diagnostic criteria [21]. RLS was diagnosed when a patient met all International Restless Legs Syndrome Study Group (IRLSSG) criteria [22,23]. LMR was diagnosed when subjects had the compelling urge to move extremities, but not fulfilling one of the other essential features including worsening of symptoms during periods of rest or inactivity, partial or total relief by movement and worsening of symptoms in the evening or at night, thus LMR is not according with the minimal RLS criteria [2]. Patients presenting with atypical Parkinsonism or cognitive impairment (Mini-Mental Status Examination (MMSE) score lower than 24 (higher than middle school cultural level) or lower than 20 (primary school level) or lower than 17 (illiteracy)) were excluded from the study. All subjects are of ethnic Han. The study was approved by the Institution's Ethics Committee and all recruited patients consented to participate in the study.

2.2. Examination program

We interviewed patients face to face and recorded demographic information, history, symptoms, medications, general neurologic and medical examinations, and MMSE for all recruited patients. Patients considered positive for RLS and LMR were examined again by another investigator, and were further assessed with a unified semi-structured questionnaire for leg restlessness symptoms, age of RLS/LMR onset, a RLS family history, anatomical distribution of leg restlessness, and if RLS/LMR symptoms related with motor fluctuations and seasonal exacerbation. RLS/LMR severity for one week prior to interview was assessed using the International RLS rating scale (IRLSRS) [24]. Due to our previous experience that leg restlessness may present with disequilibrium features during the whole year and may relate with seasonal trends, we recorded RLS/LMR occurrence in detail and average weekly RLS/LMR frequency was assessed according to item 7 of IRLSRS [24]. All patients with any leg restlessness underwent laboratory and neurophysiological examinations (hemoglobin, glucose, renal function, iron, ferritin, transferrin, vascular ultrasound, nerve conduction velocities and electromyography) to exclude known causes of secondary RLS such as anemia, chronic renal failure, rheumatoid arthritis, peripheral polyneuropathies, diabetes, venous stasis, and vascular claudication. For polyneuropathies, we diagnosed on the basis of clinical findings with diffuse peripheral nerve involvement in the distal limbs and we hadn't excluded patients with subclinical neuropathy revealed by electrophysiological study but without symptoms of peripheral neuropathy. Those with medication history of neuroleptics, anxiolytics and antidepressants or sleep medication were also excluded for confounding RLS mimic symptoms.

Other assessments included H&Y stage and Unified Parkinson's Disease Rating Scale motor scale (UPDRS III) during "on" to evaluate severity of PD, Hamilton Depression Scale (HAMD) and Parkinson's Disease Sleep Scale-II (PDSS-II) to assess depressive symptoms (cutoff point ≥ 8) and sleep status in part of PD patients (Table 3). We calculated twice for the duration and dosage of dopaminergic medication according to the time point at interview and the time of RLS/LMR onset, respectively. Levodopa equivalent dosage (LED) for dopaminergic drugs were calculated as described previously [25]. All PD patients with RLS/LMR completed the above questionnaires for PD evaluation. For PD patients without RLS/LMR, one of every two patients according to attendance number completed all above questionnaires for assessment of PD profile.

2.3. Statistical analysis

Data were analyzed using SPSS 21.0 for Windows (IBM Co., USA). All data are presented as means ± standard deviations. Since most of the variables were not normally distributed, the Kruskal–Wallis test was used for all single variable comparisons, and followed by a post hoc Mann–Whitney test when $P < 0.05$. Differences in proportions were analyzed by Pearson Chi-Square or Fisher's Exact Test when appropriate. P-values less than 0.05 were considered statistically significant.

3. Results

276 PD patients agreed to participate in the study, 6 were excluded due to cognitive impairment, and 8 were excluded due to atypical Parkinsonism during subsequent follow-up, leaving 262 eligible PD patients, including 135 male subjects (51.5%) and 127 female subjects (48.5%). The average age was 68.3 ± 10.2 years old. Mean duration of PD was 4.8 ± 4.2 years and mean age of PD onset was 63.4 ± 10.8 years.

We also recruited 61 patients diagnosed with RLS, 8 of whom were excluded due to secondary causes. Thus a total of 53 iRLS patients were eligible for analysis including 18 male subjects (34.0%) and 35 female subjects (66.0%).

3.1. Incidence of RLS and LMR in PD patients

A total of 69/262 PD patients reported some leg restlessness, but 23 patients (12 RLS, 11 LMR) were excluded due to possible secondary factors for RLS or RLS mimic symptoms and were subsequently eliminated from statistical evaluation. Thus, 28/262 (10.7%) were diagnosed with RLS and 18/262 (6.9%) were diagnosed with LMR. When compared with PD/RLS patients, PD/LMR patients had shorter duration of leg restlessness ($P < 0.01$), lower scores of IRLSRS ($P < 0.01$), lower H&Y stage and lower PDSS-2 ($P < 0.05$). [Tables 1, 2].

3.2. Comparison of PD patients with RLS or LMR versus PD patients without restlessness

Both PD/RLS and PD/LMR patients had younger age of PD onset ($P < 0.01$). PD/RLS patients had higher H&Y stage and UPDRSIII scores during "on" than "pure" PD patients ($P < 0.01$), furthermore, PD/RLS patients also had higher UPDRSIII subscores of Parkinsonism in limb ($P < 0.01$), bradykinesia ($P < 0.01$) and rigidity ($P < 0.01$). We didn't find severity or frequency of RLS (IRLSRS or IRLSRS item 7 scores) correlated with UPDRSIII scores in PD patients with RLS ($r = -0.270$, $P > 0.05$; $r = 0.077$, $P > 0.05$). When calculated on time of RLS/LMR onset, PD patients with RLS or LMR had less total daily LED, LED-dopa, LED-DA and a shorter duration of dopaminergic medication than PD patients without leg restless. However, no statistic differences were found when calculated on time of interview. Also, PD patients with RLS had higher PDSS-2 scores ($P < 0.01$) [Table 1].

3.3. Comparison of leg restlessness in PD patients with RLS or LMR versus iRLS

Compared with iRLS patients, PD/RLS and PD/LMR patients were of older age both at interview and RLS/LMR symptom onset ($P < 0.01$). More iRLS developed RLS symptom before 40 years old and two even before 10 years old. However, only one PD/RLS had RLS symptom onset before 40 years old who was the only PD/RLS with a positive RLS family history. 3 PD/RLS patients developed RLS preceded PD onset including the one with a positive RLS family history [Table 2].

Both PD/RLS and PD/LMR patients had more unilateral or unilateral dominant leg restlessness compared with iRLS patients ($P < 0.01$), and most of the asymmetrical RLS/LMR symptoms are ipsilateral to the more effected Parkinsonism side. More PD/RLS and PD/LMR patients reported that their RLS or LMR symptoms worsened in winter ($P < 0.01$), while iRLS patients often had their RLS symptoms aggravated in summer ($P < 0.05$). Only 2/18 (11.1%) of the PD/LMR patients had their symptom of leg restless aggravated at evening or at night while the

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